NIAID Bethesda, MD USA	**POLICY**	Version No: 2.0 Date: November 20, 2007 Page 1 of 8
	Effective Date: February 11, 2008 Release Date: January 31, 2008	

Title: **NIAID PRINCIPLES FOR USE OF A DATA AND SAFETY MONITORING BOARD (DSMB) FOR OVERSIGHT OF CLINICAL TRIALS**

APPROVAL

	Approving Entity	**Date**
Approval Mechanism:	***NIAID Executive Committee (ExCom)***	***Jan, 24, 2008***

1.0 PURPOSE

1.1 This policy provides instructions for Data and Safety Monitoring Board (DSMB) operations within the NIAID.

2.0 BACKGROUND

2.1 NIH Policy requires data and safety monitoring for all NIH funded clinical trials. Since the policy issuance, Divisions within the Institute have each established policies, procedures, guidelines etc to implement and comply with the general NIH policy. While some program variances may be appropriate/necessary, a proposal for some harmonization of key issues across Divisions was put forth at the 2005 NIAID Winter Program Retreat. A Working Group representing all Divisions collected and analyzed data on Data and Safety Monitoring Board practices. The conclusions of the Group are put forth as the principles below.

3.0 SCOPE

3.1 This policy applies to all NIAID Divisions (intramural and extramural) and Center(s) conducting clinical research studies under the oversight of a Data and Safety Monitoring Board.

4.0 RESPONSIBILITIES

4.1 Division Directors, Deputy Directors, Branch Chiefs, and/or other staff as designated are responsible for the dissemination of this policy for implementation to staff responsible for DSMB operations. Policy guidance dissemination should include, but not be limited to, investigators, DSMB members, the DSMB Executive Secretary and support staff, DSMB statisticians, and drug company or other sponsors as appropriate.

4.2 The Division of Clinical Research (DCR) will be responsible to review and update this policy as needed based on new/revised NIH policy or federal regulations. The NIAID Executive Committee will approve future revisions to this policy.

5.0 DSMB PRINCIPLES

5.1 “Data and safety monitoring board" refers to a committee of experts, independent of the trial investigators, pharmaceutical sponsor (if any), and funding agency, which periodically reviews the conduct and results of the trial and recommends continuation without change, continuation with change, or termination of the trial. The primary consideration is for the safety of trial participants, broadly understood to include the possible consequences of receiving an intervention already conclusively shown to be inferior.

DSMB summary recommendations are reported to the sponsor who then submits them to the study chair and NIAID lead. Institutional Review Boards (IRBs) / Ethics Committees (ECs) then receive these summary recommendations from their respective investigators. The responsible official makes the final decision to accept them or not, after consulting with the trial leadership and relevant staff. A decision to reject a recommendation should be communicated to the DSMB with appropriate rationale.

It is a requirement that the DSMB voting members include a biostatistician experienced in statistical methods for clinical trials and a clinician with expertise in the relevant clinical specialty under study. Representatives of other clinical or laboratory specialties, bioethics, and the affected community (but not trial participants) are often critically important. Selection of DSMB members should include consideration of clinical trials experience, relevant expertise, prior DSMB service and absence of significant conflict of interest. For clinical trials supported primarily by NIAID, NIAID staff will appoint members. DSMB membership should reflect NIAID’s commitment to diversity.

It is best to introduce the trial to the DSMB before beginning enrollment. The DSMB should understand, before seeing interim results, how the investigators want to approach the possibility of early stopping for safety, futility, and efficacy reasons.

5.2 The hallmark of oversight by a DSMB is a strict limit on access to interim results according to study arm. This applies to both safety and efficacy results. Comparative results are presented to the DSMB in closed reports and closed sessions seen/attended only by voting members of the DSMB and one member of the NIAID staff or contractor serving as DSMB executive secretary (apart from the statistician who prepared the reports, who may be a member of the NIAID

staff or a contractor to NIAID). These provisions will not limit the ability of the DSMB to invite any person to participate in any part of the meeting if it believes the person has important information or knowledge that will assist the DSMB in fulfilling its responsibilities. Exceptions to restricted access to closed report interim results, which should be rare, are addressed below.

If information from ongoing review of individual adverse event reports and summaries, or emerging information external to the trial raises concern about safety of current or future trial participants, the Medical Officer may request access to the safety information in the closed report in a manner that minimizes unblinding. The Medical Officer may also request permission to attend part of the DSMB closed session dealing with safety analyses. A written request for access to closed safety reports and attendance at the DSMB session dealing with safety analyses should be reviewed and approved by the Division Director. Division Directors are strongly encouraged to consult with the DSMB chair before approving a request. This provision refers only to the possibility of an identified potential physical or social harm, not to a broad concern regarding the qualifications or experience of investigators.

Under most circumstances, neither the designated NIAID Medical Officer/Medical Monitor nor any other NIAID program official will receive efficacy analyses or attend the part of the DSMB closed session dealing with these analyses. In certain rare circumstances, exceptions to this policy may be granted by the NIAID Deputy Director for Clinical Research and Special Projects.

In other scenarios where DSMBs have documented significant deficiencies in closed data reports that impact their ability to perform an adequate review, a Division may need to provide support to the study statistician in order to maintain the integrity of the trial. Access to draft closed reports in these specific cases may be granted by the NIAID Deputy Director for Clinical Research and Special Projects to a qualified independent reviewer when needed to ensure quality of reports prior to DSMB submission. The independent reviewer will not perform any study safety monitoring functions, have any interactions with the study team, or be a member of the Program or Branch sponsoring the study. This reviewer may consult with a representative of DSMB if needed to ensure that concerns of the Board are being fully addressed, but otherwise will have no interactions with the DSMB. Ideally, the Division should explore options of having the site contract directly with a qualified expert in lieu of an NIAID employee or contractor serving in this role. (In this scenario, a request for exception to policy

would not be needed.) This type of exception should be requested only in critical situations where trial integrity could be compromised; future long-term solutions need to be actively explored.

5.3 Traditionally, and for purposes of this policy, clinical trials requiring DSMB oversight are randomized, multi-center, Phase III and Phase IV trials and large randomized Phase II trials. Other trials may be designated for DSMB oversight for specific programmatic reasons. For trials of interventions at early stages of development, the structure of the traditional DSMB, while acceptable, may not be ideal. For example, arranging meetings or conference calls on short notice to discuss the report of a very serious and unanticipated problem may be very difficult. When a fully independent DSMB is not necessary, the investigator, with approval of NIAID, is expected to implement an alternative plan - such as a safety monitoring committee - meeting the spirit of the goals of enhancing participant safety and the objectivity of interpreting data. (To avoid confusion, the name "data and safety monitoring board" should only be used for structures as described herein.)

Each DSMB should operate according to provisions of a formal charter, agreed to in advance by NIAID, the investigators, and the DSMB. Charters should address appointment of members, scheduling and format of meetings, distribution and disposition of meeting materials, preparation of meeting summaries and written recommendations, management of conflict of interest, and other procedural matters.

6.0 REFERENCES/LINKS

6.1 Supercedes: Policy Version 1.0 (August 11, 2006)

6.2 The below online information is current as of the effective date of this policy.

NIH POLICY FOR DATA AND SAFETY MONITORING (June 10, 1998)
http://grants.nih.gov/grants/guide/notice-files/not98-084.html

GUIDANCE ON REPORTING ADVERSE EVENTS TO INSTITUTIONAL REVIEW BOARDS FOR NIH-SUPPORTED MULTICENTER CLINICAL TRIALS (June 11, 1999)
http://grants1.nih.gov/grants/guide/notice-files/not99-107.html

FURTHER GUIDANCE ON A DATA AND SAFETY MONITORING FOR PHASE I AND PHASE II TRIALS (June 5, 2000)
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
http://www.fda.gov/cber/gdlns/clintrialdmc.htm

6.3 Other References:

DeMets, DL, Furberg, CD, Friedman, LM (editors) (2006) *Data Monitoring in Clinical Trials: A Case Studies Approach*. Springer, New York.

Ellenberg, SS, Fleming, TR, DeMets, DL (2003) *Data Monitoring Committees in Clinical Trials.* John Wiley & Sons Ltd, West Sussex, England.

7.0 INQUIRIES/CONTACT INFORMATION

7.1 For questions or comments please contact NCRSexec.sec.@niaid.nih.gov

8.0 AVAILABILITY

8.1 This policy is available on the DCR website. Hard copy documents are filed in the DCR office.

9.0 ATTACHMENTS

9.1 Attachment A – List of Working Group Members

10.0 REVIEW SCHEDULE/CHANGE SUMMARY

10.1 This policy will be reviewed an annual basis. Interim revisions will be made as needed to comply with NIH or other federal regulatory changes and/or at the request of the DCR Director.

10.2 The change summary table below will be updated when the document is reviewed or revised.

Version #	Date	Replaces	Date of Review/Revision	Rationale for Revision/Retirement
2.0	11/20/07	1.0	11/20/07	Clarification enhancements; addition of procedures for access to closed safety data and new special exceptions for data access

ATTACHMENT A

DSMB Principles Document Working Group
Member List

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